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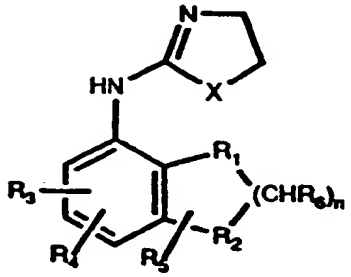
(54) Title: USE OF 2-(2-ALKYLPHENYLAMINO)-OXAZOLINES, -THIAZOLINES AND -IMIDAZOLINES AS ALPHA 2 ADRENERGIC AGENTS

(57) Abstract

A pharmaceutical composition, useful for treating animals of the mammalian species, including humans, to treat diseases and conditions which normally respond to treatment with alpha$_2$ adrenergic agents, contains as its active alpha$_2$ adrenergic agent ingredient one or more compounds of formula (I) where X is O, S or NH; n is an integer with the values of 0, 1 or 2; when n is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms; when n is 1 or 2, then R_1 and R_2 both are methylene (CH_2), or methylene substituted with an R_5 group where R_5 is lower alkyl of 1 to 6 carbons; R_3 and R_4 independently are H or lower alkyl having 1 to 6 carbons; R_6 is H or lower alkyl of 1 to 6 carbons.



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Use of 2-(2-alkylphenylamino)-oxazolines,-thiazolines and -imidazolines as alpha 2 adrenergic agents

1. Field of the Invention

The present invention is directed to pharmaceutical compositions which have adrenergic effects, and which comprise as active ingredients one or more 2-(2-alkyl-phenylamino)-oxazoline, 2-(2-alkylphenylamino)-thiazoline or 2-(2-alkylphenylamino)-imidazoline compounds. The pharmaceutical compositions are useful for treating or preventing conditions in animals of the mammalian species which normally respond to treatment by adrenergic agents. Thus, the pharmaceutical compositions of the inventions are useful as agents for altering the rate of fluid flow in the gastrointestinal tract (anti-diarrhetic), anti-spastic, anti-hypertensive, anti-ischemic, anti-epileptic, agents for increasing fluid flow in at least one kidney (diuretic) anesthetic, memory-enhancing agents and as sleeping aids. In another aspect, the present invention is directed to administering such formulations and compositions to animals of the mammalian species (including humans) for treating the above-noted diseases and conditions.

2. Brief Description of Background Art

Adrenergic agents, and particularly agents affective on α_2 adrenergic receptors are known in the art. For example, United States Patent No. 5,091,528 describes 6- or 7-(2-imino-2-imidazolidine)-1,4-benzoxazines as α adrenergic agents. Published European Patent Application 0 251 453 describes certain

cyclohexyl substituted amino-dihydrooxazoles, -thiazoles and -imidazoles as α_2 adrenergic agents. United States Patent No. 3,598,833 describes 2-cycloalkylamino oxazolines having local anesthetic, sedative, vasoconstrictory, mucous membrane de-swelling, blood pressure depressant and gastric fluid secretion inhibitory effects. Further United States and foreign patents and scientific publications which pertain to substituted amino-oxazolines, imidazolines and thiazolines are as follows:

United States Patent No. 4,587,257 [2-(trisubstituted phenylimino)imidazoline compounds capable of controlling ocular bleeding];

United States Patent No. 3,636,219 [2-(substituted-phenylamino)-thiazolines and imidazolines having anticholinergic activity];

United States Patent No. 3,453,284 [2-(substituted-anilino)-2-oxazolines;

United States Patent No. 3,432,600 [partially reduced 2-(naphtylamino) oxazolines and indanylamino oxazolines;

United States Patent No. 3,679,798 [compositions comprising arylaminooxazolines and an antocholigeneric agent];

United States Patent No. 3,624,092 [amino-oxazolines useful as central nervous system depressants];

United States Patent No. 2,876,232 [2-(9-fluorenylamino)-oxazolines,) and German Patent Nos. 1,191,381 and 1,195,323, and European Patent Application No. 87304019.0.

United States Patent No. 4,515,800 [2-(trisubstituted phenylimino)imidazoline compounds, also

known as 2- (trisubstituted-anilino)-1,3-diazacyclopentene-(2) compounds, treatment of glaucoma].

United States Patent No. 5,066,664 [2-(hydroxy-2-alkylphenylamino)-oxazolines and thiazolines, anti-glaucoma and vasoconstrictive agents].

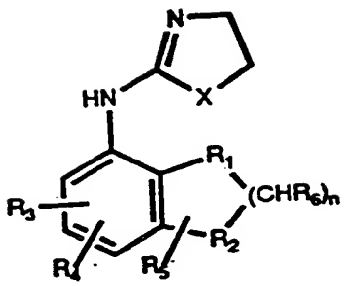
Chapleo et al. in Journal of Medicinal Chemistry, 1989 32, 1627 -1630 describe heteroaromatic analogues of clonidine as partial agonists of α_2 adrenoreceptor.

United States Patent No. 5,151,440 describes ophthalmic compositions suitable for lowering intraocular pressure, comprising compounds of substantially the same structure as the compounds used as adrenergic agents in the present invention.

As it will become apparent from the ensuing description, some of the "composition of matter" used in the novel pharmaceutical compositions and methods of administration of the present invention are described or mentioned in one or more of the above-listed references, but the activity of these compounds as adrenergic agents, and especially as agents acting on the α_2 adrenergic receptor is believed to be novel to the present invention.

SUMMARY OF THE INVENTION

The present invention covers pharmaceutical compositions, which comprise as active α_2 adrenergic agents one or more compounds having the formula



FORMULA 1

where X is O, S or NH; n is an integer with the values of 0, 1 or 2; when n is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms; when n is 1 or 2, then R_1 and R_2 both are methylene (CH_2), or methylene substituted with an R_5 group where R_5 is lower alkyl of 1 to 6 carbons; R_3 and R_4 independently are H or lower alkyl having 1 to 6 carbons; R_6 is H or lower alkyl of 1 to 6 carbons. The pharmaceutical compositions, containing one or more of the above-defined compounds as active ingredients, are administered to animals of the mammalian species for the purpose of treating or preventing one or more of the diseases or conditions which are known to respond to α_2 adrenergic agents. Thus, the pharmaceutical compositions of the invention are administered to animals of the mammalian species, including humans, as agents for altering the rate of fluid transport in the gastrointestinal tract (anti-diarrhetic), as anti-spastic, anti-hypertensive, anti-ischemic, anti-epileptic agents, as agents for increasing renal fluid flow in at least one kidney (diuretic), as anesthetic, or memory-enhancing agents and as sleeping aids.

General Embodiments

Definitions

The term "alkyl" as used here refers to and includes normal and branch chained alkyl groups as well as cyclo-alkyl groups. The term "lower alkyl", unless specifically stated otherwise, includes normal alkyl, branch chained alkyl as well as cyclo-alkyl groups having 1 to 6 carbon atoms.

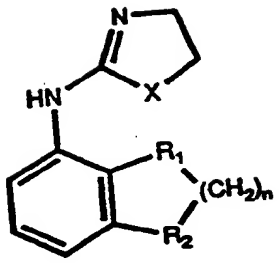
A pharmaceutically acceptable salt may be prepared for any compound of this invention having a functionality capable of forming such salt, for example an acid or an amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

Such a salt may be derived from any organic or inorganic acid or base. The salt may be a mono or polyvalent ion. Of particular interest where the acid function is concerned are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic amine salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as mono-, di- or tri-acid may also

be used.

With reference to **Formula 1**, in the compounds which are preferably incorporated into the pharmaceutical compositions or formulations of the present invention, and which are used in the method of administering such formulations to animals and humans as α_2 adrenergic agents, preferably the R_3, R_4 and R_6 groups are H. Preferably **n** is zero, and in that case the R_1 and R_2 groups preferably both are independently from one another, lower alkyl having 1 to 3 carbons. Compounds are also preferred where one of the R_1 and R_2 groups is lower alkyl, and the other is H. Active agents in the novel pharmaceutical compositions and in the novel method of administration of the present invention are also preferred where, in accordance with **Formula 1**, **n** is 2 and the R_1 and R_2 groups both are CH_2, there is no R_5 substituent and R_6 is H. Preferably, the active compounds in the composition and method of administration of the present invention are oxazoline and imidazoline derivatives; i.e. preferably in **Formula 1 X** is O or NH.

Most preferred as active agents in the novel compositions and methods of administration of the present invention are oxazoline or imidazoline compounds where: R_3 and R_4 are both H, and (1) **n** is 0 and R_1 and R_2 both are CH_3, or at least one the R_1 and R_2 groups is CH_3 and the other is H; or (2) **n** is 2 and R_1 and R_2 both are CH_2, there is no R_5 substituent and R_6 is H. The compounds which are most preferred as active ingredients in the composition and method of administration of the present invention, in accordance with the foregoing, are illustrated in **Formula 2**:



Formula 2

Compound 1 X=O n=0, R_1=R_2=CH_3,

Compound 1a X=O n=0, R_1=CH_3, R_2=H,

Compound 2 X=O n=2, R_1=R_2=CH_2,

Compound 3 X=NH n=0, R_1=R_2=CH_3,

Compound 3a X=NH n=0, R_1=CH_3, R_2=H, and

Compound 4 X=NH n=2, R_1=R_2=CH_2.

The present compounds are useful to provide one or more desired therapeutic effects in a mammal, as noted above. Among the desired therapeutic effects are an alteration, preferably a decrease, in the rate of fluid transport in the gastrointestinal tract of a mammal (anti-diarrhea effect), and an increase in the renal fluid flow in at least one kidney of a mammal (diuretic effect), in addition to the other affects which are genereally recognized in the art to be caused by α_2 adrenergic compounds. Thus, for example, the present compounds are effective as anti-diarrhea agents, and/or a medication for use in the treatment or management of kidney disease, as anti-spastic, anti-hypertensive, anti-ischemic, anti-epileptic, memory-enhancing agents and as sleeping aids.

Any suitable method of administering the present

compound or compounds to the mammal to be treated may be used. The particular method of administration chosen is preferably one which allows the present compound or compounds to have the desired therapeutic effect in an effective manner, e.g., low medication concentration and low incidence of side effects. In many applications, the present compound or compounds are administered to a mammal in a manner substantially similar to that used to administer other alpha agonists, in particular α_2 agonists, to obtain the same or a similar therapeutic effect.

The present compound or compounds may be included in a medication composition together with one or more other components to provide a medication composition which can be effectively administered. Such other components, e.g., carriers, anti-oxidants, bulking agents and the like, may be chosen from those materials which are conventional and well known in the art, e.g., as being included in medication compositions with α_2 agonists. Whereas the effective dose of the compounds of the present compositions will depend on the nature of the host mammal and the specific diesease or condition treated it is anticipated that an effective daily dose of the compounds is in the range of 1 microgramm - 10 mg per kg/body weight of the host. The ability of the compounds within the present invention to bind strongly and selectively to α_2 adrenergic receptors in preferance over α_1 adrenergic receptors was confirmed by the following assay procedures which are generally recognized in the art to provide pertinent information with respect to the adrenergic activity of the compounds assayed: $alpha_1$ (human brain) assay, $alpha_2A$ (HT-29 cells) assay, and $alpha_2B$ (rat

kidney) assay. A description of these assay procedures is as follows.

Receptor Binding Assays

Membrane preparation: Membrane suspensions were prepared from human cerebral cortex (HCC), HT-29 cells (HT) and rat kidney cortex (RtKC), as applicable. Tissues were homogenized in iced-cold buffer [250 mM sucrose, 5 mM tris, pH 7.4 (RtKC), or 50 mM Tris-HCl, 5 mM EDTA, pH 7.4 (HCC, HT)] with a Polytron homogenizer for 30 secs at setting #7, and centrifuged for 10 minutes at 300 x g at 4°C. The supernatant was diluted 1:2 with 50 mM Tris-HCl buffer, pH 7.4 (RkCC, HCC) or pH 8.0 (HT) then centrifuged at 49,000 x g for 15-20 minutes. The pellet fraction was washed 3 times (resuspended in Tris-HCl buffer and centrifuged for 15-20 minutes at 49,000 x g). The pellet was then stored at -80°C until the binding assay.

Binding studies: The radioligands [^{3}H] rauwolscine (specific activity 80 Ci/mmol) and [^{3}H] prazosin (specific activity 77 Ci/mmol) were obtained from New England Nuclear, Boston, MA. Frozen membrane pellet was resuspended in glycine glycine buffer, pH 7.6. Membrane protein homogenate (150 - 300 µg) was incubated with radioligand under the following conditions: 22 °C, 30 minutes (HCC, HT), 0°C, 120 minutes (RtKC), in a final volume of 500 µl. At the end of the incubation period, the samples were filtered through glass fiber filters (Whatman GF/B) in a 96-well cell harvester and rapidly washed four times with 4 mls of iced-cold 50 mM Tris-HCl buffer. The filters were then oven dried and transferred to scintillation vials containing 5 mls of Beckman's Ready Protein^R scintillation cocktail for counting. Non-specific

binding was defined by 10 μM phentolamine. Protein concentrations were determined with a protein assay kit from Bio Rad. Binding isotherms, equilibrium dissociation and affinity constants were analyzed and determined by the non-linear least squares curve fitting program AccuFit Competition/Saturation by Beckman.

As it will be recognized by those skilled in the art from the forogoing descriptions, the described assays are radioligand assays which measure the binding of the test compound to the respective α_1 or α_2 receptor. The K_i value which is calculated from these tests is called the "affinity constant" and is related to the concentration (expressed in nanomolar) of the test compound which displaces 50 % of the radioligand from the receptors.

The results of these assays with examplary compounds within the scope of the invention are shown in the following Table where the column "α_1Ki" refers to K_i values (in nanomolar) obtained in the $Alpha_1$ (human brain) Assay, the column "α_2AKi" refers to K_i values obtained in the $Alpha_2A$ (HT-29 cells) Assay, and the column "α_2BKi" refers to K_i values obtained in the $Alpha_2B$ (rat kidney) Assay.

TABLE

Compound #	α_1 K_i	α_2A K_i	α_2B K_i
1	1,211	5.1	8.5
1a	7,401	35.7	208.4
2	1,629	2.2	6.2
3	434	5.8	1.5
3a	2,171	7.5	25.3

As is well known in the art, in the foregoing assays a K_i value which is approximately 100 nanomolar

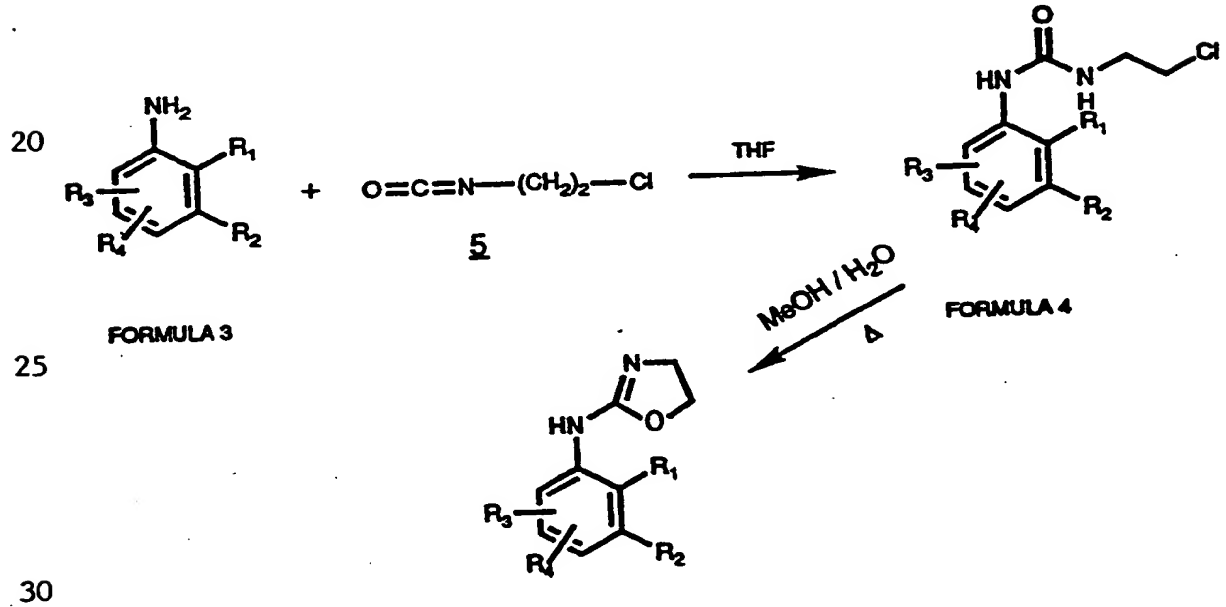
or less indicates that the compound is active. A compound which has a K_i value of 10 or less is considered very active. In accordance with these criteria, the compounds used in accordance with the present invention are not active on the α_1 adrenergic receptors, but are active on the α_2 adrenergic receptors, and therefore can be considered specific (or highly selective) to the α_2 adrenergic receptors.

Specific Embodiments

The compounds which were found in accordance with the present invention to be active α_2 adrenergic agents can be made by a number of different synthetic chemical pathways. To illustrate the invention, there is here outlined a series of steps which have been proven to provide the active compounds of **Formula 1**, when such synthesis is followed in fact and in spirit. The synthetic chemist will readily appreciate that the speciifc conditions set out here can be generalized to any and all of the compounds represented by **Formula 1**. Furthermore, the synthetic chemist will readily appreciate that the herein described synthetic steps may be varied and or adjusted by those skilled in the art, to obtain the active compounds used in the novel pharmaceutical composition and method of administration of the present invention.

Active oxazoline compounds (in **Formula 1** X=O) used in the pharmaceutical compositions and methods of administration of the present invention, where n=0 and where R_1 is lower alkyl of 1 to 6 carbons, R_2 is H or lower alkyl of 1 to 6 carbons, and where R_3 and R_4 are defined as above in connection with **Formula 1**, can be synthesized in accordance with the generalized procedure shown in **R action Scheme 1**.

As a first step of this reaction sequence, an aniline derivative corresponding to **Formula 3** (where R_1 is lower alkyl of 1 to 6 carbons, R_2 is H or lower alkyl of 1 to 6 carbons, and where R_3 and R_4 are defined as in connection with **Formula 1**) is reacted with chloroethylisocyanate (**Compound 5**, a commercially readily available reagent). The reaction between compounds of **Formula 3** and chloroethylisocyanate (**Compound 5**) is typically conducted in a neutral solvent, such as tetrahydrofuran (THF) and may be conducted at room temperature or at elevated temperature. In the event the aniline derivative (compound of **Formula 3**) is added to the reaction as a hydrochloride (or like) salt, an acid acceptor (such as triethylamine) may also be added to the reaction mixture.



FORMULA 3

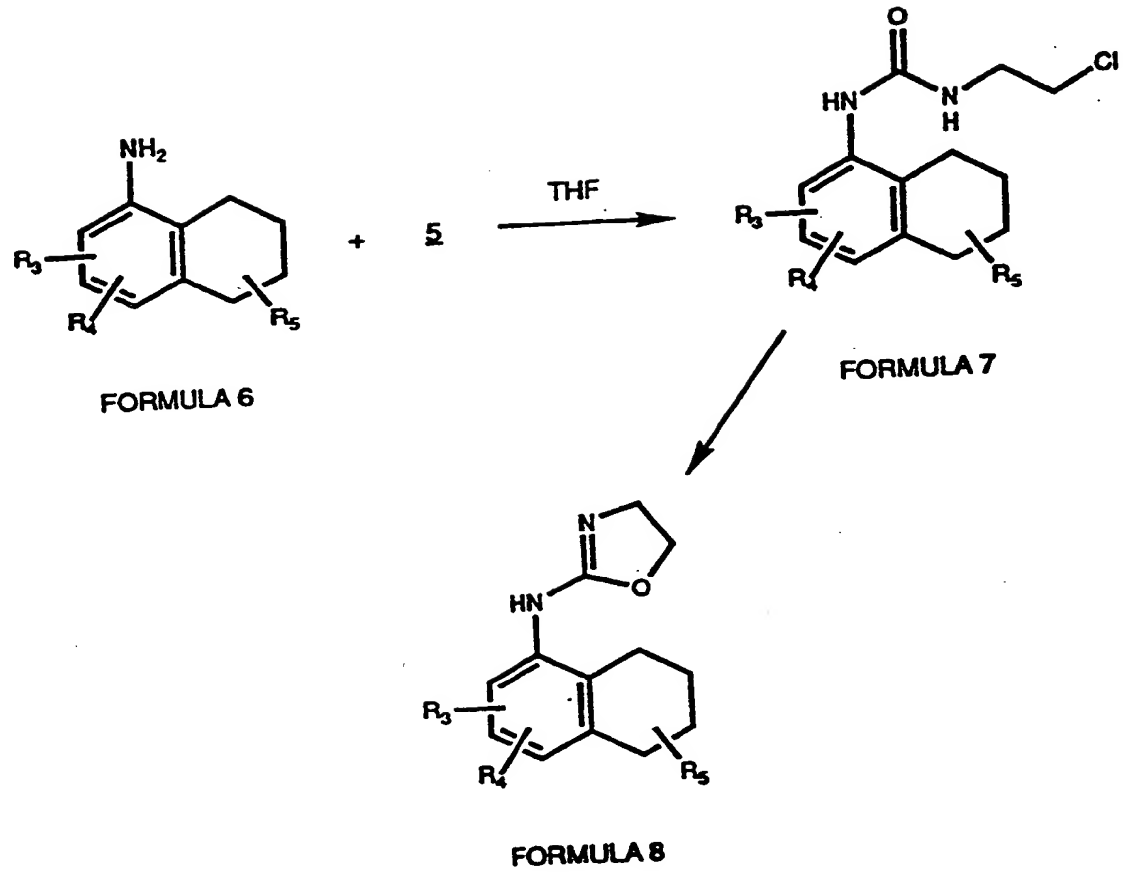
FORMULA 4

FORMULA 5

REACTION SCHEME 1

The reaction between chloroethylisocyanate (**Compound 5**) and the aniline derivative of **Formula 3** provides the intermediate chloroethylurea derivative, compound of **Formula 4** (R_1 is lower alkyl of 1 to 6 carbons, R_2 is H or lower alkyl of 1 to 6 carbons, and where R_3 and R_4 are defined as above in connection with **Formula 1**). The chloroethylurea derivative (**Formula 4**) typically precipitates out of the reaction mixture, and is isolated, for example by vacuum filtration. Generally speaking, the chloroethylurea derivative (**Formula 4**) can be adequately characterized and used in the next reaction without further purification.

The chloroethylurea derivative (**Formula 4**) is cyclized to provide the desired 2-(alkylphenylamino) oxazolines (**Formula 5**) by heating, preferably in an aqueous medium, such as a solvent mixture containing water and a lower alkohol, preferably methanol. Typically, the desired 2-(alkylphenylamino) oxazoline (**Formula 5**) obtained in the cyclization reaction, is isolated from the reaction mixture by first concentrating the same to remove the solvents, and thereafter by extraction in halogenated organic solvent (such as methylene chloride) followed by evaporation of the organic solvent. The desired product may also be recrystallized to attain further purity. The desired 2-(alkylphenylamino) oxazolines (**Formula 5**) may also be isolated from the cyclization reaction as the corresponding hydrochloride (or other) salt. For preparation of 2-(alkylphenylamino) oxazolines in general, and of **Compound 1** in particular, further reference is made to United States Patent No. 3,453,284, the specification of which is expressly inc rporated herein by reference.



FORMULA 6

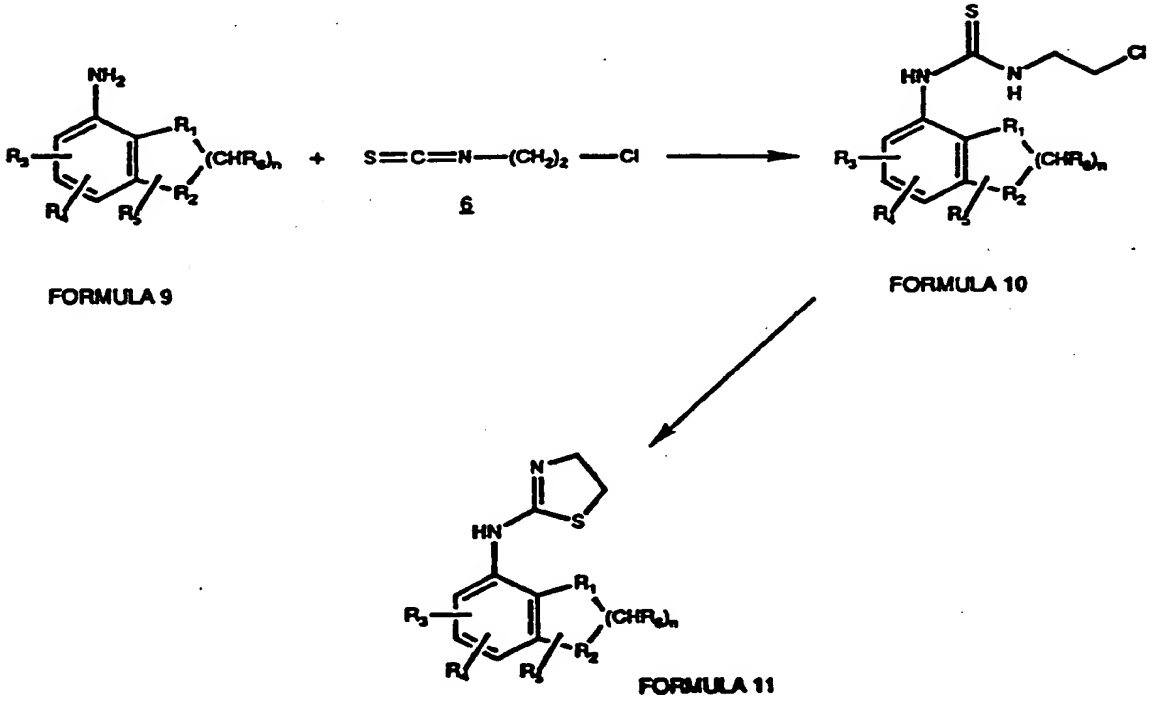
FORMULA 7

FORMULA 8

REACTION SCHEME 2

2-(5,6,7,8-Tetrahydronaphtylamino)-oxazoline derivatives (in **Formula 1** X=O n=2), which in accordance with the present invention are active α_2 adrenergic agents in mammals, can be made from the corresponding 5,6,7,8-tetrahydronaphtyl-1-amine, or substituted 5,6,7,8-tetrahydronaphtyl-1-amine, (compounds of **Formula 6**) by reaction with chloroethylisocyanate (**Compound 5**) as illustrated in **Reaction Scheme 2**. The conditions of this reaction are substantially similar to the analogous reaction described above with reference to **Reaction Scheme 1**. The resulting chloroethylurea intermediates (compounds of **Formula 7**)

are cyclized into the desired 2-(5,6,7,8-tetrahydronaphtylamino)-oxazoline derivatives (**Formula 8**) by heating in a polar solvent, such as aqueous methanol. In Formulas 6, 7 and 8 the symbols R_3, R_4 and R_5 are defined as in connection with **Formula 1**. For preparation of 2-(5,6,7,8-tetrahydronaphtylamino)-oxazoline derivatives in general, and of **Compound 2** in particular, further reference is made to United States Patent No. 3,432,600, the specification of which is expressly incorporated herein by reference.

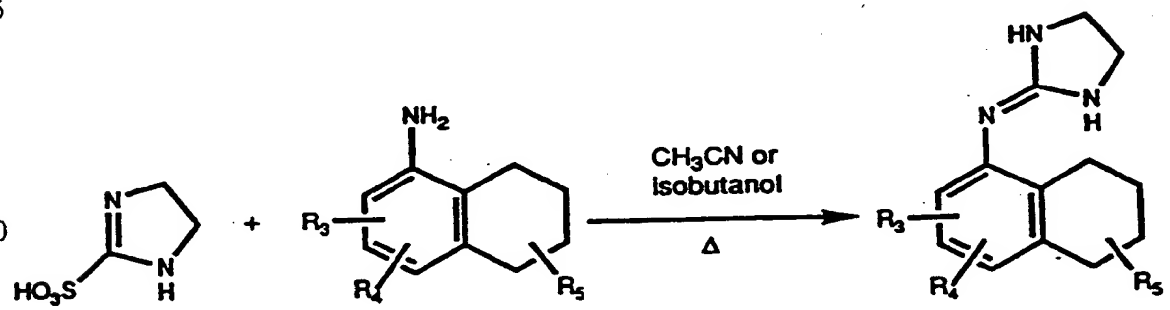


REACTION SCHEME 3

2-(2-Alkylphenyl-amino)-thiazolines (i. e. compounds where in **Formula 1** X=S) which are active in accordance with the present invention as α_2 adrenergic agents in mammals, can be synthesized in a reaction sequence which is analogous to the reaction sequences outlined above for the corresponding oxazoline derivatives; the only significant difference being that in the first step of the sequence chloroethylisothiocyanate (**Compound 6**) is used (instead of chloroethylisocyanate, **Compound 5**). Thus, referring to generalized **Reaction Scheme 3**, an alkyl substituted aniline corresponding to **Formula 9** is reacted with chloroethylisothiocyanate (**Compound 6**) in a suitable solvent, (such as tetrahydrofuran) to provide the intermediate chloroethylthiourea (**Formula 10**). The symbols **n** and R_1 through R_6 in the formulas illustrated in **Reaction Scheme 3** are defined as above with reference to **Formula 1**. In this connection it is noted that **Formula 9** embraces substituted and unsubstituted 5,6,7,8-tetrahydro-1-naphtylamines, and that, in this specification with reference to the aromatic moiety of the active compounds used in the invention, the terms an "alkyl substituted phenyl" or "alkyl substituted aniline" broadly cover 5,6,7,8-tetrahydronaphtyl derivatives as well. Referring still to **Reaction Scheme 3** the intermediate chloroethylthiourea (**Formula 10**) is cyclized, typically in an aqueous solvent mixture (e. g. H_2O and CH_3OH) at room temperature or by gentle heating, to provide the desired 2-(2-alkylphenyl-amino)-thiazolines (**Formula 11**).

2-(2-Alkylphenyl-imino)-imidazolidines (i. e. compounds of **Formula 1** where X=NH) which have been discovered in the present invention to be active as α_2

adrenergic agents in mammals, can be synthesized, generally speaking, by the reaction of imidazoline-2-sulfonic acid (**Compound 7**) with an appropriately substituted aniline. Imidazoline-2-sulfonic acid (**Compound 7**) can be made in accordance with the procedure described in the chemical literature, (e. g. U.S. Patent No. 4,656,291) from 2-imidazolidinethione (**Compound 8**). The synthetic steps leading to 2-(5,6,7,8-tetrahydro-1-naphtylimino)-imidazolidines [2-(5,6,7,8-tetrahydro-1-naphtylamino)-imidazolines] and to 2-(alkylphenylimino)-imidazolidines [2-(alkylphenylamino)-imidazolines], respectively, are illustrated in generalized **Reaction Schemes 4** and **5**.

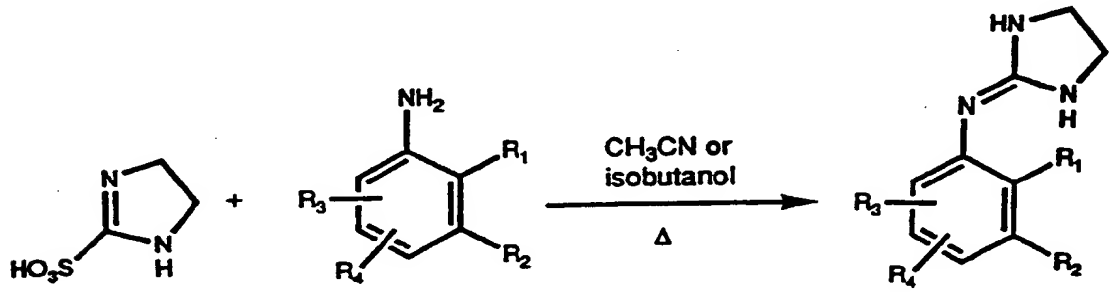


I FORMULA 6 FORMULA 12

REACTION SCHEME 4

Thus, with specific reference to **Reaction Scheme 4**, imidazoline-2-sulfonic acid (**Compound 7**) is heated under pressure in a solvent (e. g. acetonitrile) with a substituted or unsubstituted 5,6,7,8-tetrahydronaphtyl-

1-amine (**Formula 6**), to provide the 2-(5,6,7,8-tetrahydro-1-naphtylimino)-imidazolidine derivatives of **Formula 12**. The symbols R_3, R_4 and R_5 in **Formula 12** are defined the same as in **Formula 6**.



Z FORMULA 3 FORMULA 13

REACTION SCHEME 5

Reaction Scheme 5 illustrates the synthesis of 2-(alkylphenylimino)-imidazolidine derivatives (**Formula 13**) where, with reference to **Formula 1** X=NH and n=0. In this synthesis a substituted aniline of **Formula 3** is heated under pressure with imidazoline-2-sulfonic acid (**Compound 7**). In **Formula 13** the symbols R_1, R_2, R_3 and R_4 are defined as in connection with **Formula 3**. For further description of the synthesis of compounds of **Formula 13**, reference is made to United States Patent No. 4,515,800, the specification of which is expressly incorporated herein.

Specific Examples

2-(2,3-Dimethylphenylamino)-oxazoline (Compound 1)

Chloroethylisocyanate (Compound 5, Aldrich, 346 mg, 3.3 mmol) was added to a stirred solution of 2,3-dimethylaniline (Aldrich, 400 mg, 3.3 mmol) in tetrahydrofuran (5 ml) at room temperature. After 30 minutes a white precipitate formed. The solid chloroethylurea was collected by vacuum filtration yield: 477 mg (64 %): mp 145-146° C. HNMR (300 MHz, $CDCl_3$) σ 7.00 (m, 3H); 6.72 (br, 1H); 5.19 (br, 1H), 3.59 (m, 2H); 3.49 (m, 2H); 2.30 (s, 3H); 2.18 (s, 3H); Mass spectrum m/e 226.0872 ($C_1H_{15}ClN_2O$ requires 226.0872). The chlorethylurea (199 mg, 0.88 mmol) was suspended in H_2O (4 ml) and CH_3 OH (4 ml) and heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1N NaOH (to pH 13). The organic layer was dried over Na_2CO_3 and concentrated in vacuo to yield 140 mg (84%) of the title compound as a white crystalline solid: mp 112-113.5° C; ^1H NMR (300 MHz, $CDCl_3$) σ 7.19 (m, 1H); 7.09 (m, 1H), 6.91 (m, 1H); 5.00 (br, s, 1H); 4.40 (t, 2H); 3.70 (t, 2H); 2.30 (s, 3H); 2.15 (s, 3H); Mass spectrum m/e 190.1104 ($C_{11}H_{14}N_2O$ requires 190.1106).

2-(2-methylphenylamino)-oxazoline (Compound 1a)

Chloroethylisocyanate (Compound 5, Aldrich, 440 mg, 4.2, mmol, 356 μl) was added dropwise to a stirred cold (0°) solution of ortho toluidine 500 mg, 4.66 mmol, 496 μl) in tetrahydrofuran (5 ml). After 15 minutes the reaction mixture was allowed to warm to room temperature. After one hour at room temperature a precipitate (solid chloroethylurea) was coll cted by filtration and washed with cold tetrahydrofuran.

Yield: 872 mg (98 %).

The chloroethylurea (202 mg, 0.95 mmol) was dissolved in a mixture of methanol (7 ml) and water (5 ml) and the solution was refluxed for 4 hours. Then brine solution (2 ml) was added and the reaction mixture was extracted with diethyl ether. The reaction mixture was therafter made basic to ph 14 by addition of 2.5 N sodium hydroxide solution, and was extracted with ethyl acetate. The ethyl acetate layer was dried (K_2CO_3) and evaporated to drynes to yield the title compound, as a white solid (173 mg, approx 100 %). Also see U. S Patent No. 3,453,284.

Following a substantially similar procedure and starting with the corresponding substituted aniline, the following additional examples of compounds of the invention can be synthesized, and utilized in the novel adrenergic compositions and methods of administration of the present invention:

2-(2,3-diethylphenylamino)-oxazoline;

2-(2-methyl-3-ethylphenylamino)-oxazoline;

2-(2-ethyl-3-methylphenylamino)-oxazoline;

2-(2,3,4-trimethylphenylamino)-oxazoline;

2-(2,3,5-trimethylphenylamino)-oxazoline;

2-(2,5,6-trimethylphenylamino)-oxazoline;

2-(5,6,7,8-tetrahydronaphthylamino)-oxazoline

(Compound 2)

Chloroethylisocyanate (**Compound 5** 210 mg, 2.05 mmol) was added to a stirred solution at 5,6,7,8-tetrahydro-1-naphthylamine (302 mg, 2.05 mmol) in tetrahydrofuran (2 ml). After 30 minutes the resulting chloroethylurea was collected by vacuum filtration. Yield: 302 mg (58%) of fine white crystals: mp 101-103°; H NMR (300 MHz, $CDCl_3$) σ 6.98 - 7.30 (m, 3H);

6.08 (brs, 1H); 5.19 (br, s, 1H); 3.68 (m, 2H); 3.55 (m, 2H); 2.79 (m, 2H); 2.61 (m, 2H); 1.80 (m, 4H); Mass spectrum m/e 252.1034 ($C_{13}H_{17}ClN_2O$ requires 252.1029). The chloroethyl urea (237 mg, 0.94 mmol) was suspended in H_2O (3 ml) and CH_3OH (3 ml) and heated to reflux for 18 hours. The reaction mixture was cooled to room temperature and worked up as above to yield after re-crystallization (hexane/$CHCl_3$) 187.6 mg (87%) of the title compound: mp 160-162°C; ^1H NMR (300 MHz, $CDCl_3$) σ 7.23 (m, 1H); 7.08 (m, 1H; 6.75 (m, 1H); 5.55 (br, 1H); 4.35 (t, 2H); 3.70 (t, 2H); 2.70 (m, 2H); 2.58 (m, 2H); 1.80 (m, 4H); Mass spectrum m/e 216.1257 ($C_{13}H_{16}N_2O$ requires 216.1262).

Following a substantially similar procedure and starting with the corresponding substituted 5,6,7,8-tetrahydronaphtyl-1-amine, the following additional examples of compounds of the invention can be synthesized, and utilized in the novel adrenergic compositions and methods of administration of the present invention:

2-(2-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(3-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(4-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(5-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(6-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(7-methyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline;

2-(8-methyl-5,6,7,8-tetrahydronaphthylamino)-

oxazoline;
2-(2-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(3-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(4-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(5-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(6-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(7-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(8-ethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,3-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,4-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(3,4-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,5-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,6-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,7-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(2,8-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(3,5-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;
2-(3,6-dimethyl-5,6,7,8-tetrahydronaphthylamino)-
oxazoline;

2-(3,7-dimethyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline, and

2-(3,8-dimethyl-5,6,7,8-tetrahydronaphthylamino)-oxazoline.

2-(5,6,7,8-Tetrahydro-1-naphthylimino)-imidazolidine (**Compound 4**)

Preparation of imidazoline-2-sulfonic acid: 2-Imidazolidinethione (**Compound 8**, Aldrich, 66.3 g, 650 mmol), Na_2MoO_4(5g, 227 mmol) and NaCl (15 g. 256 mmol) were added to 300 ml H_2O. Although some dissolution occurred, a solid residue remained in the liquid of the mixture. The mixture was cooled to -10° C using an immersion cooler. 500 ml of a 30% (w/v) aqueous H_2O_2 solution was placed in a jacketed controlled drop rate addition funnel and cooled to 0°C using an ice/H_2O bath. The aqueous H_2O_2 solution was added to the mixture at a rate of 60 drops/min. The mixture was stirred for 16 hours at -10°C. During this time, the mixture changed from a white suspension to a dark blue solution to a light blue suspension. At the end of 16 hours, a solid was filtered from the suspension and dried in vacuo. No further purification was needed. Yield: 57.8 g (a yield of 52.3%) of the title compound as a white solid mp 157-159°C; H NMR (300 MHz, DMSO d_6) σ 10.38 (br, 2H); 3.85 (s, 4H). This solid was stable when stored in the dark at 0°C for at least 6 months.

2-(5,6,7,8-tetrahydro-1-naphthylimino)-imidazolidine (**Compound 4**):

5,6,7,8-Tetrahydro-1-naphthylamine (Aldrich, 159 mg, 1.06 mmol), imidazoline-2-sulfonic acid (147.0 mg, 1.0 mmol, **Compound 7** obtained as described above) and CH_3CN (5ml) were placed in a thick-walled cap which was

sealed with a TEFLON™ screw and heated to 155°C for 1.25 hours. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resident was dissolved in $CHCl_3$ and washed with aq. 1N NaOH)to pH 13). The organic layer was separated, washed with brine, dried over Na_2CO_3 and concentrated in vacuo to yield a brown oil. The crude material was purified by flash chromatography (SiO_2; 80:20 $CHCl_3/CH_3OH$ saturated with NH_3) to yield 29.5 mg (14%) of the title compound as a white solid: mp 138-141°C; H NMR (300 MHz, $CDCl_3$) σ 7.05 (t, 1H) 6.82 (m, 2H); 5.41 (br, 2H); 3.50 (s, 4H); 2.79 (m, 2H); 2.62 (m, 2H); 1.80 (m, 4H); Mass spectrum m/e 214.1339 ($C_{13}H_{16}N_3$ requires 214.1344).

Following a substantially similar procedure and starting with the corresponding substituted 5,6,7,8-tetrahydronaphtyl-1-amine, the following additional examples of compounds of the invention can be synthesized, and utilized in the novel adrenergic compositions and methods of administration of the present invention:

2-(2-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(3-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(4-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(5-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(6-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(7-methyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(8-methyl-5,6,7,8-tetrahydronaphthylimino)-

imidazolidine;
2-(2-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(3-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(4-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(5-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(6-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(7-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(8-ethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,3-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,4-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(3,4-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,5-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,6-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,7-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(2,8-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(3,5-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;
2-(3,6-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine;

2-(3,7-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine; and

2-(3,8-dimethyl-5,6,7,8-tetrahydronaphthylimino)-imidazolidine.

2-(2,3-Dimethylphenylimino)-imidazolidine (**Compound 3**)

2,3 Dimethylaniline (Aldrich, 236 mg, 1.95 mmol), imidazoline-2-sulfonic acid (292 mg, 1.95 mmol, (**Compound 7** obtained as described above) and CH_3CN (4ml) were placed in a thick-walled glass tube and sealed with a TEFLON™ screw-cap. The reactants were heated to 155°C for 6 hours. The reaction was worked up as described for **Compound 4** and chromatographed (SiO_2; 70:30 $CHCl_3/CH_3OH$ saturated with NH_3) to yield a light yellow oil which was recrystallized (hexane/isopropanol to yield 61 mg (17%) of the title compound as an off-white crystalline solid: mp 141-144°C; H NMR (300 MHz, $CDCl_3$) σ 6.98 (m, 1H); 6.80 (m, 2H), 5.31 (br, 2H); 3.42 (s, 4H); 2.31 (s, 3H); 2.12 (s, 3H); Mass spectrum m/e 189.1259 ($C_{11}H_{15}N_3$ requires 189.1266). Alternatively, and preferably alcohols, most preferably isobutanol, are used instead of CH_3CN in this reaction.

2-(2-methylphenylimino)-imidazolidine (**Compound 3a**);

Ortho toluidine (536 mg, 531 μl, 5 mmol) and imidazoline-2-sulfonic acid (750 mg, 5 mmol, (**Compound 7** obtained as described above)) and CH_3CN (6ml) were heated in a thick-walled glass tube at 150°C for 16 hours. The reaction mixture was then cooeld to 0° and made basic to pH 14 by addition of 2.5 N NaOH salution. The mixture was extracted with methylene chloride, the combine extracts were died (K_2CO_3) and evaporated to dryness. Flash chromatography on silica gel yielded

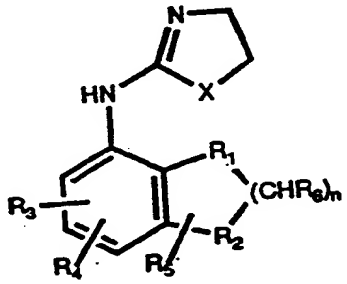
the title compound as a tan colored solid (47.0 mg, 5.37 %).

Following a substantially similar procedure and starting with the corresponding substituted aniline, the following additional examples of compounds of the invention can be synthesized, and utilized in the novel adrenergic compositions and methods of administration of the present invention:

2-(2,3-diethylphenylimino)-imidazolidine;
2-(2-methyl-3-ethylphenylimino)-imidazolidine;
2-(2-ethyl-3-methylphenylimino)-imidazolidine;
2-(2,3,4-trimethylphenylimino)-imidazolidine;
2-(2,3,5-trimethylphenylimino)-imidazolidine;
2-(2,5,6-trimethylphenylimino)-imidazolidine.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition useful for activating adrenergic receptors in a mammal, the composition comprising as its active ingredient an effective amount of one or more compounds of the formula



where **X** is O, S or NH;

n is an integer with the values of 0, 1 or 2;

R_3 and R_4 independently are H or lower alkyl having 1 to 6 carbons;

R_6 is H or lower alkyl of 1 to 6 carbons, with the proviso that when **n** is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms, when **n** is 1 or 2, then R_1 and R_2 both are CHR_5, where R_5 independently is H or lower alkyl of 1 to 6 carbons, or salts of compounds of said formula.

2. The pharmaceutical composition of Claim 1 wherein in the formula of the active ingredient **X** is O.

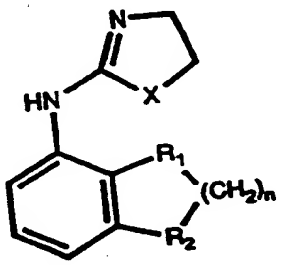
3. The pharmaceutical composition of Claim 1 wherein in the formula of the active ingredient **X** is S.

4. The pharmaceutical composition of Claim 1 wherein in the formula of the active ingredient **X** is NH.

5. The pharmaceutical composition of Claim 1 wherein in the formula of the active ingredient R_1 and R_2 independently are H or CH_3 and n is zero.

6. The pharmaceutical composition of Claim 1 wherein in the formula of the active ingredient n is 2.

7. A pharmaceutical composition adapted for administering to a mammal having a disease or condition which is treated with agents for altering the rate of fluid flow in the gastrointestinal tract, anti-spastic, anti-hypertensive, anti-ischemic, anti-epileptic agents, or with agents for increasing fluid flow in at least one kidney, or with anesthetic, memory-enhancing or sleeping aid agents, the composition comprising as its active ingredient an effective amount of one or more compounds of the formula



where X is O, S or NH;

n is an integer with the values of 0, 1 or 2, with the proviso that when n is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms, when n is 1 or 2, then R_1 and R_2 both are CH_2, or salts of compounds of said formula.

8. The pharmaceutical composition of Claim 7 wherein in the formula of the active ingredient X is O.

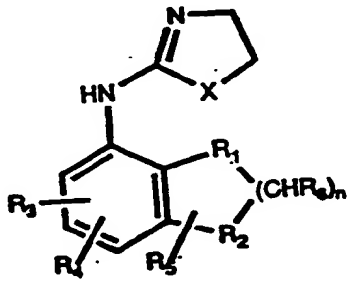
9. The pharmaceutical composition of Claim 7 wherein in the formula of the active ingredient X is S.

10. The pharmaceutical composition of Claim 7 wherein in the formula of the active ingredient X is NH.

11. The pharmaceutical composition of Claim 7 wherein in the formula of the active ingredient R_1 and R_2 independently are H or CH_3 and n is zero.

12. The pharmaceutical composition of Claim 7 wherein in the formula of the active ingredient n is 2.

13. A method of treating diseases or conditions of an animal of the mammmalian species, the disease or condition being of the type which responds to treatment with $alpha_2$ adrenergic agents, the method of treatment comprising the steps of administering to the mammal a pharmaceutical composition which comprises as its active ingredient an effective amount of one or more compounds of the formula



where X is O, S or NH;
n is an integer with the values of 0, 1 or 2;

R_3 and R_4 independently are H or lower alkyl having 1 to 6 carbons;

R_6 is H or lower alkyl of 1 to 6 carbons, with the proviso that when n is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms, when n is 1 or 2, then R_1 and R_2 both are CHR_5, where R_5 independently is H or lower alkyl of 1 to 6 carbons, or salts of compounds of said formula.

14. The method of treatment of Claim 13 wherein in the formula of the active ingredient n is zero.

15. The method of treatment of Claim 14 wherein in the formula of the active ingredient X is O.

16. The method of treatment of Claim 14 wherein in the formula of the active ingredient X is NH.

17. The method of treatment of Claim 14 wherein in the formula of the active ingredient X is S.

18. The method of treatment of Claim 13 wherein in the formula of the active ingredient n is 2.

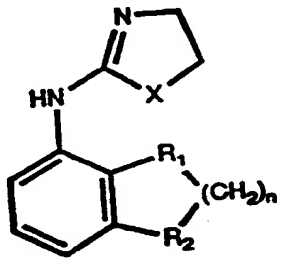
19. The method of treatment of Claim 18 wherein in the formula of the active ingredient X is O.

20. The method of treatment of Claim 18 wherein in the formula of the active ingredient X is NH.

21. The method of treatment of Claim 34 wherein in the formula of the active ingredient X is S.

22. A method of treating animals of the mammmalian species, which are afflicted with a disease or condition of the type which is treated with an α_2 adrenergic agent having effect of altering the rate of fluid flow in the gastrointestinal tract, or anti-spastic, anti-hypertensive, anti-ischemic, anti-epileptic, anesthetic, memory-enhancing or sleep aiding effect, or the ffect of increasing fluid flow in at

least one kidney, the method of treatment comprising the steps of administering to the mammal a pharmaceutical composition which comprises as its active ingredient an effective amount of one or more compounds of the formula



where X is O, S or NH;

n is an integer with the values of 0, 1 or 2, with the proviso that when n is 0 then R_1 is lower alkyl having 1 to 6 carbon atoms and R_2 is H or lower alkyl having 1 to 6 carbon atoms, when n is 1 or 2, then R_1 and R_2 both are CH_2, or salts of compounds of said formula.

23. The method of treatment of Claim 2 wherein in the formula of the active ingredient n is zero.

24. The method of treatment of Claim 23 wherein in the formula of the active ingredient X is O.

25. The method of treatment of Claim 23 wherein in the formula of the active ingredient X is NH.

26. The method of treatment of Claim 23 wherein in the formula of the active ingredient X is S.

27. The method of treatment of Claim 2 wherein in the formula of the active ingredient n is 2.

28. The method of treatment of Claim 27 wherein in the formula of the active ingredient X is O.

29. The method of treatment of Claim 27 wherein in the formula of the active ingredient X is NH.

30. The method of treatment of Claim 27 wherein in the formula of the active ingredient X is S.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 94/12015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/42 A61K31/425 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 151 440 (GLUCHOWSKI) 29 September 1992 cited in the application see the whole document ---	1-12
X	GASTROENTEROLOGY, vol.86, no.1, 1984 pages 120 - 128 K. DHARMSATAPHORN ET AL. 'Effects of structure-activity relationships of alpha adrenergic compounds on electrolyte transport in the rabbit ileum and rat colon.' * introduction; discussion * ---	1,4,6,7, 10,12, 13,16, 18,20, 22,27,29
A	US,A,5 066 664 (GLUCHOWSKI) 19 November 1991 cited in the application --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 1995	07.03.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

Form PCT/ISA/218 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat al Application No
PCT/US 94/12015

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 636 219 (CULICK ET AL.) 18 January 1972 cited in the application	
A	US,A,4 587 257 (DESANTIS ET AL.) 6 May 1986 cited in the application	
A	US,A,4 515 800 (CAVERO ET AL.) 7 May 1985 cited in the application	

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/12015

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13-30 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[illegible] l Application No
PCT/US 94/12015

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5151440	29-09-92	US-A-	5252595	12-10-93
US-A-5066664	19-11-91	NONE		
US-A-3636219	18-01-72	NONE		
US-A-4587257	06-05-86	EP-A-	0236636	16-09-87
		AU-B-	585309	15-06-89
		AU-A-	5322486	06-08-87
US-A-4515800	07-05-85	CA-A-	1201066	25-02-86
		CA-C-	1194418	01-10-85
		EP-A,B	0081924	22-06-83
		JP-C-	1772159	14-07-93
		JP-B-	4053846	27-08-92
		JP-A-	58116417	11-07-83
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